REMARKS

The present invention relates to the use of bone marrow stromal cells to rescue a mammal from a lethal dose of total body irradiation.

Claims 1-16 and 33-48 have been canceled herein without prejudice to the inclusion of the subject matter contained therein in any later filed continuation and/or divisional application(s). Claims 17, 21, 25 and 29-32 have been amended herein to recite "short-term culture." Therefore claims 17-32 are pending and under consideration following entry of the present Amendment.

Support for amendments to claims 17, 21, 25 and 29-32

Applicants assert that the as-filed specification amply supports the amendment to the claims with respect to the term short-term culture, and as such does not add new matter. Although the term "short-term" is not explicitly recited in the as-filed specification, one skilled in the art would be able to infer, based upon the disclosure of the instant application, that the cells of the present invention are short-term cultured cells. The amendment to the claims to recite short-term is consistent with the Examiner's suggestion found on page 9 of the present Final Office Action.

As set forth in MPEP §2163, "While there is no *in haec verba* requirement, newly added claim limitations must be supported in specification through express, implicit, or inherent disclosure." Applicants respectfully argue that the specification more than adequately supports a short-term culture. The as-filed specification describes a method of culturing a mixed population of bone marrow cells, containing both adherent and non-adherent cells, isolated from an allogeneic donor, wherein the population of adherent cells are separated from non-adherent cells. The adherent population of cells, which are referred to by the specification as bone marrow stromal cells, are cultured for a period of time (e.g. no more than the third passage) prior to the administration to an irradiated mammal. Therefore, it can be inferred based upon the as-filed specification that the cells of the present invention are short-term cultured cells by virtue of culturing the cells for no more than the third passage. Beginning on page 9 of the specification, it is disclosed that the bone marrow stromal cells are administered to a mammal upon isolation or following a period of *in vitro* culturing. Further, the specification beginning on page 15 discloses that the isolated bone marrow stromal cells are cultured *in vitro* prior to transplantation

into a mammal and that the cells used for transplantation were allowed to reach the third passage. As such, the amendment to the claims is supported by the specification, and no new matter has been added.

Applicants respectfully submit that the amendment to the claims comply with the written description requirement as set forth under 35 U.S.C. §112, first paragraph. In the landmark case of *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991), the Court of Appeals for the Federal Circuit traced the development of the written description requirement under 35 U.S.C. §112, first paragraph. The *Vas-Cath* Court, in a unanimous opinion, noted approvingly that in a written description analysis, "[t]he primary concern is factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." *Vas-Cath*, 19 USPQ2d at 1116 (quoting *In re Wertheim*, 191 USPQ 90, 96 (C.C.P.A. 1976)) (emphasis added). After discussing the policy reasons underlying the requirement, the Court set forth the standard for the written description requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use;" the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. . . . The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter."

Vas-Cath, 19 USPQ2d at 1117 (emphasis added) (quoting *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985)). Therefore, it is well-settled that the knowledge of those skilled in the art informs the written description inquiry.

In determining the sufficiency of support in a disclosure with respect to the written description requirement, "it is not necessary that the application describe the claimed invention in *ipsis verbis*; all that is required is that it reasonably convey to persons skilled in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him." *In re Edwards*, 196 USPQ 465, 467 (C.C.P.A. 1978) (citing *In re Lukach*, 169 USPQ 795 (C.C.P.A. 1971); *In re Driscoll*, 195 USPQ 434 (C.C.P.A. 1977)). More recently, in *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983), the Court of Appeals for the Federal Circuit, citing *In re Edwards*, emphasized:

> The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language. (Emphasis added).

In addition, in *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit pointed out that literal support is not required in order to satisfy the written description requirement:

> If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met. For example, in *Ralston Purina Co. v. Far-Mor-Co., Inc.*, 227 USPQ 177, 180 (Fed. Cir. 1985), the trial court admitted expert testimony about known industry standards regarding temperature and pressure in "the art of both farinaceous and proteinaceous vegetable materials." The effect of the testimony was to expand the breadth of the actual written description since it was apparent that the inventor possessed such knowledge of industry standards of temperature and pressure at the time the original application was filed. (Emphasis added).

Therefore, it is clear that the invention need not be described in *ipsis verbis*, *i.e.*, literally, for purposes of the written description requirement under 35 U.S.C. §112, first paragraph. Rather, what is needed is that the skilled artisan understand, based upon the disclosure in the specification as filed and the knowledge imputed to the skilled artisan at the time the specification was filed, that the inventor had possession of the claimed subject matter.

Applicants respectfully submit that the skilled artisan would have understood, based upon the disclosure provided in the specification as filed, that the inventors had possession of the invention claimed in the amended claims. Claims 17, 21, 25 and 29-32 have been amended herein to recite "short-term cultured cells." As discussed above, support for this claim is in the as-filed specification.

Rejection of claims 1-16 and 33-48 under 35 U.S.C. § 112, first paragraph - written description

The Examiner has rejected claims 1-16 and 33-48 under 35 U.S.C. § 112, first paragraph for lacking written description. Specifically, the Examiner asserts that the amendment to the claims with respect to the recitation of "not modified in any way" and "cultured *in vitro* for approximately five weeks" adds new matter. Applicants do not agree with the Examiner.

However, in order to expedite the prosecution of this application, Applicants have canceled claims 1-16 and 33-48 without prejudice to the inclusion of the subject matter contained therein in any later filed continuation and/or divisional application(s). As such, the rejection to these claims under 35 U.S.C. § 112, first paragraph for lacking written description is moot and should be withdrawn.

Rejection of claims 1-48 pursuant to 35 U.S.C. §103(a)

The Examiner has rejected claims 1-48 pursuant to 35 U.S.C. § 103(a), as being obvious over Anklesaria et al. (1987, Proc. Natl. Acad. Sci., USA 84:7681-85), in view of Palsson et al. (U.S. Patent No. 5,635,386). The Examiner has also cited Shpall et al. (1997, Annu. Rev. Med. 48:241-51) and Remes et al. (1996, Annals Medicine 28:79-81) to demonstrate the state of the field at the time of the filing date of the present application. Specifically, the Examiner contends that Palsson teaches the use of human hematopoietic stem cells and their cultures that "afford improved methods for bone marrow transplantation," and the combination of the teachings of Anklesaria with Palsson would arrive at the present invention. Applicants respectfully traverse this rejection for the following reasons.

As an initial matter, claims 1-16 and 33-48 have been canceled herein. Therefore, the rejection of these claims under 35 U.S.C. § 103(a) is moot.

Applicants submit that Anklesaria in view of Palsson cannot render claims 17-32 *prima facie* obvious under 35 U.S.C. §103(a). Anklesaria does not teach the invention and Palsson cannot cure the deficiencies of Anklesaria as discussed elsewhere herein. Applicants contend that Anklesaria teaches a long-term culture and Palsson merely teaches hematopoietic stem cells.

> More specifically, the MPEP states, in relevant part:
>
> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

None of these criteria have been met here.

The first prong of the *In re Vaeck* test, the requirement that the references themselves or the knowledge in the art must provide some suggestion or motivation, has not been met in this instance. Applicants assert that Anklesaria offers no suggestion or motivation to modify the reference or to combine reference teachings to arrive at the present invention. Even if Anklesaria did in some way, which it does not, offer a suggestion or motivation to combine the references, Applicants contend that the combined teachings would teach away from the present invention. As discussed elsewhere herein, Anklesaria does not teach the use of bone marrow stromal cells cultured for no more than the third passage or otherwise a short-term culture *per se*. Rather, Anklesaria teaches a virally transformed stable clonal cell line (GB1/6), which was establish from the adherent layer of long-term marrow cultures (LBMCs) from B6Cast mice. As such, Anklesaria does not suggest Applicants' cells. Nowhere does Anklesaria offer a suggestion or motivation to use Applicants' cells for rescuing a mammal from total body irradiation.

It was widely known in the art at the time of filing this application that a stable cell line from a mouse, and moreover a transformed cell line, has many characteristics of a malignant cell. Therefore, the GB1/6 cell line taught by Anklesaria is distinct from cells that are cultured for no more than the third passage (otherwise known as short-term cultures). Specifically, human bone marrow stromal cells do not become stable cell lines or otherwise transformed/immortalized by way of culturing the cells for no more than the third passage. That is, a cell that is isolated from a mammal and cultured for no more than the third passage has a limited life span in culture and typically stops growing after several passages (e.g. replicative senescence) unless the cell is modified in some manner to generate a transformed/immortalized cell.

Anklesaria teaches a cell line generated from a long-term marrow culture. The Examiner agrees that Anklesaria does not teach a cell that is cultured for no more than the third passage. However the Examiner contends that a long-term cultured cell renders a cell cultured for no more than the third passage obvious. In fact the Examiner contends that passing the cells only serves to expand the cells to a desired cell number. However, the Examiner seems to overlook the fact that long-term cultures and short-term cultures are inherently different. That is, cells in long-term cultures have been modified in a way that allows for the continued growth of the cells without entering replicative senescence.

At the time of the priority date of the present application, long-term cultures were used as a source of an unlimited supply of cells. The use of long-term cultures over short-term cultures in the art is exemplified in Anklesaria and Palsson. In fact, Applicants made reference to the use of long-term cultures in the art as set forth in the background of the invention. Prior to the present invention, long-term cultures were widely used because of the number of cells that can be obtained. However, the present invention provides an advantage over the use of immortalized cells that have unstable genotypes and genetic mutations for enhancing recovery of hematopoiesis in mammals having ablated marrow. The present invention offers an improvement and relates to an unexpected result that short-term cultures (bone marrow stromal cells cultured for no more than the third passage) can be used in lieu of long-term cultures per se or transformed cell lines to provide a therapeutic benefit *in vivo*. The cells of the present invention have not been genetically modified in anyway to render them immortalized. It appears that the Examiner has overlooked this aspect of the invention.

Based on the teachings of Anklesaria, the skilled artisan would be motivated to not use Applicants' cell, but rather use a long-term clonal cell line. In fact, Anklesaria used the specific GB1/6 cell line of Anklesaria because this cell line was chosen based on its endothelial-like characteristics and *in vitro* support capacity for multipotential hematopoietic progenitor cells. Anklesaria points out on page 7685, second paragraph that "other clonal stromal cell lines do not support multipotential hematopoietic progenitor cells forming CFU-S *in vitro*." Based on the teachings of Anklesaria, not all clonal cell lines are useful to support hematopoietic recovery after irradiation. Only the GB1/6 cell line was useful in generating a therapeutic effect and therefore a skilled artisan would be motivated to use only the specific GB1/6 cell line.

In addition, the Examiner is combining teachings of bone marrow stromal cells via Anklesaria with teachings of hematopoietic stem cells and bone marrow transplantation via Palsson to render the present invention as encompassed in claims 17-32 *primia facie* obvious. Applicants respectfully point out to the Examiner that a bone marrow stromal cell is different from a hematopoietic stem cell and for that matter, transplantation of bone marrow stromal cells is different from bone marrow transplantation. Therefore, the combination of Anklesaria with Palsson is improper because each reference teaches a different cell type.

For example, hematopoietic stem cells have the ability to differentiate into blood cells, whereas bone marrow stromal cells are at least multipotent (e.g. having the ability to

differentiate into at least bone, cartilage, and fat). One skilled in the art would not have been motivated to combine the teachings of Anklesaria and Palsson, and even if the artisan did combine the references, the combined teachings would not point the artisan to the present invention.

Palsson merely teaches hematopoietic stem cells and long term bone marrow culture conditions. Nowhere does Palsson teach short-term cultures or for that matter bone marrow stromal cells cultured for no more than the third passage.

Palsson relates to the discovery of novel methods, including culture media conditions, for *in vitro* culturing of human stem cells and promoting division and/or the optimization of growing human hematopoietic progenitor cell (see column 7, line 18-22). Moreover, Palsson teaches in the Example section, particularly Example 1, long-term culture conditions and kinetics of non-adherent cell population (hematopoietic progenitor cells). Table 1 summarizes the average number of non-adherent progenitor cells removed from long term bone marrow cultures as a function of the medium perfusion rate and inoculum density. The remaining Examples relate to optimizing culture conditions for growing hematopoietic progenitor cells (non-adherent) *in vitro*. Nowhere does Palsson teach administering bone marrow stromal cells, yet alone administering bone marrow stromal cells that are cultured for no more than the third passage to a mammal for a therapeutic effect. Applicants respectfully remind the Examiner that non-adherent hematopoietic progenitor cells are distinct from adherent bone marrow stromal cells. Applicants respectfully point out that administration of hematopoietic cells or for that matter bone marrow transplantation is different from administration of bone marrow stromal cells.

The Examiner asserts that based on Palsson, if expansion was not required, the isolated cells may be administered immediately upon isolation and therefore would render bone marrow stromal cells cultured for no more than the third passage obvious. Such a statement by the Examiner appears to be an unreasonable interpretation of the teachings of Palsson. As an initial matter, Palsson relates to optimizing the culture conditions for non-adherent cells (hematopoietic progenitor cells). Teachings on non-adherent cells cannot render adherent cells (bone marrow stromal cells) obvious. Furthermore, Palsson teaches long-term bone marrow cultures. Nowhere does Palsson discloses administering bone marrow stromal cells to a mammal.

On the contrary, in column 10, lines 29-32, Palsson discloses that bone marrow stromal cells may or may not be present in the cultures of his invention. Palsson states that in typical cultures, stromal cells are present in cell culture in an amount of approximately 10^{-3} to 10^{-1} (stromal cells/total cells). Based on the teachings of Palsson, a skilled artisan would understand that Palsson cultures hematopoietic progenitor cells with bone marrow stromal cells. At best, Palsson teaches the administration of a cell mixture comprising bone marrow stromal cells and hematopoietic progenitor cells. Therefore, Palsson teaches away from the present invention. The present invention relates to administering bone marrow stromal cells without hematopoietic progenitor cells.

The second criteria for establishing a *prima facie* case of obviousness is that there must be a reasonable expectation of success. Applicants contend that based on the disclosure set forth in Anklesaria, the skilled artisan would not have any reason to expect that Applicants' cell would rescue a mammal from a lethal dose of total body irradiation. Rather, upon reading Anklesaria, a skilled artisan would only have a reasonable expectation of success for using a transformed cell line and specifically the GB1/6 cell line to rescue a mammal from a lethal dose of total body irradiation. Anklesaria states that not all clonal cell lines are useful to support hematopoietic recovery after irradiation. Only the GB1/6 cell line was useful in generating a therapeutic effect and therefore a skilled artisan would only have a reasonable expectation of success to use the specific GB1/6 cell line. Therefore, Anklesaria fails to render the present invention *prima facie* obvious because Anklesaria offers no reason to suggest that Applicants' cell would successfully rescue a mammal from total body irradiation.

It appears that the Examiner considers bone marrow transplantation and transplantation of bone marrow stromal cells to be equivalent. On page 11 of the present Final Office Action, the Examiner states that if two references disclose the same thing at the same time, they necessarily enable, and therefore provide a reasonable expectation of success for the same subject matter. Applicants contend that the Examiner cannot combine teachings of bone marrow transplantation with transplantation of bone marrow stromal cells. Bone marrow contains a mixture of cells, none of which are isolated from the mixture.

In addition, Palsson, when combined with the teachings of Anklesaria does not generate a reasonable expectation of success in rescuing a mammal from total body irradiation by administering Applicants' cell to the mammal. Palsson teaches optimal growth conditions for

culturing hematopoietic progenitors *in vitro* and long-term cultured stem cells for bone marrow transplantation. Nowhere does Palsson teach short-term cultures where the cells are cultured for no more than the third passage. One skilled in the art would have no reasonable expectation of success in combining the teaching of the two references to arrive at the present invention, wherein the cells are cultured with minimal manipulation prior to the administration to the mammal in need thereof. The combination of the references does not provide a reasonable expectation of success using the cells of the present invention for rescuing a mammal from total body irradiation.

The third prong in establishing a *prima facie* case of obviousness requires the prior art reference or references to teach or suggest all of the claim limitations. As discussed elsewhere herein, Anklesaria does not teach the cells of the present invention as encompassed by the claims and defined by the specification. Therefore, Anklesaria does not teach or suggest all embodiments of the claims. In addition, the teachings of Palsson, as discussed elsewhere herein are unable to correct the deficiencies of Anklesaria, and therefore, Anklesaria in view of Palsson, cannot render the present invention *prima facie* obvious. Rather, the combination of these references would teach away from the present invention because both Anklesaria and Palsson teach using a different cell than Applicant's cell. Accordingly, Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection pursuant to 35 U.S.C. §103(a).

The Examiner cites Shpall et al. (1997, Annu. Rev. Med. 48:241-51) and Remes et al. (1996, Annals Medicine 28:79-81) to demonstrate the state of the field at the time of the filing date of the present application. Both references teach bone marrow transplantation in general, where the bone marrow contains a mixture of cells, none of which are isolated from the mixture. At best, the references teach autologous transplantation of hematopoietic progenitor cells. Again, similar to the deficiencies of Palsson, Shpall and Remes do not teach administration of bone marrow stromal cells. Applicants contend that teachings of hematopoietic progenitor cells cannot render bone marrow stromal cells obvious.

The Examiner contends that bone marrow transplantation was known in the art. Applicants do not contend that bone marrow transplantation was not known in the art. Applicants agree that bone marrow transplantation was widely known. However, the invention is distinct from bone marrow transplantation. The invention relates to the novel discovery that a subset population of cells contained within the bone marrow (bone marrow stromal cells), upon

isolation and minimal culturing can be used to rescue a mammal from a lethal dose of total body irradiation. This is NOT "bone marrow transplantation."

For all the above reasons, Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection to claims 1-48 pursuant to 35 U.S.C. §103(a).

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that claims 17-32 are now in condition for allowance. Applicants further submit that no new matter has been added by way of the present amendment. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,

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(Date)

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Printout of ATCC definition of immortalize